ORIGINAL ARTICLE

Role of Rifaximin in Preventing the Recurrence of Hepatic Encephalopathy in Patients with Chronic Liver Disease

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ABSTRACT

Aim: To compare the frequency of recurrence of hepatic encephalopathy in cirrhotic patients treated with Rifaximin plus Lactulose versus conventional oral treatment with Lactulose alone.
Study design: Descriptive, cross-sectional.
Study Duration: June 2015 to May 2016
Settings: Department of Medicine, DHQ Hospital, Pakpatan.
Methods: A total of 98 cases of chronic liver disease with hepatic encephalopathy, 20-60 years and both genders were included. Patients with gastrointestinal hemorrhage, chronic renal insufficiency, respiratory insufficiency and anemia were excluded. Treatment group patients were advised to take tab Rifaximin 550 mg twice daily along with standard prescription i.e. Lactulose 30 to 60 ml in two to three divided doses per day. Placebo group was prescribed only conventional treatment i.e. Lactulose 30 to 60 ml in two to three divided doses per day. All patients were discharged from ward after hepatic encephalopathy Conn's score was<2. Enrolled patients were followed for 3 months at which final outcome i.e., recurrence of hepatic encephalopathy (yes/no) was noted.
Results: The mean age of patients in treatment group was 43.76±10.54 years and in placebo group were 43.65±11.13 years. Out of these 98 patients, 69(70.41%) were male and 29(29.59%) were females with ratio of 2.34:1. Recurrence of hepatic encephalopathy was seen in 09(18.37%) patients in treatment group and 22 (40.90%) patients in placebo group with p-value of 0.005.
Conclusion: This study concluded that rifaximin plus lactulose is better in reducing the recurrence of hepatic encephalopathy as compared to conventional treatment with lactulose alone.
Keywords: Hepatic encephalopathy, lactulose, rifaximin, recurrence.

INTRODUCTION

Globally 170 million people affected by hepatitis C[1]. Hepatic encephalopathy (HE) represents a continuum of transient reversiblepsychiatric and neurologic dysfunction in cases of chronic liver disease (CLD)[2]. In Cirrhotics, prevalence of HE varies from 30-45%[3].

Management of HE strategies are directed towards increased elimination and reduction of gut-derived ammonia in addition to correction of conditions that provoke HE. Lactulose, non-absorbable synthetic disaccharide syrup, is digested by the bacteria in colon to short-chain fatty acids, resulting in acidification of content of colon. This acidification favors the formation of ammonium ion in the $NH_4NH_3 + H^+$ equation; NH_4^+ is not absorbable, whereas NH_3 is absorbable and thought to be neurotoxic. Lactulose also leads to a changes in bowel flora so that fewer ammonia-forming organisms are present[1,2]. Although lactulose seems to work in the acute setting, but for durability of remission different antibiotics have to be used[4-6].

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Oral antibiotics like paromomycin, neomycin, vancomycin and metronidazole have been used to reduce the burden of ammonia form gut flora but not recommended for long term use because ofperipheral neuropathy, ototoxicity and nephrotoxicity.[4]Rifaximin is a poorly absorbed antibiotic that is thought to reduce ammonia production by eliminating ammonia-producing colonic bacteria with no systemic manifestations.

In some studies, Rifaximin found effective as compared to antimicrobials and non-absorbable disaccharides in cases of HE[4-6].

Overt episodes of HE are debilitating, can occur without any warning, render the patient incapable of self-care, and frequently result in hospitalization. Although the occurrence of episodes of HE appears to be unrelated to the cause of cirrhosis, increases in the frequency and severity of such episodes predict an increased risk of death.[9] Rifaximin has shown promising results in preventing the recurrent episodes of hepatic encephalopathy[4,5] Pakistani population is different from others in dietary habits and gut flora due to different consumption of meat when compared to western population[7], a major factor in ammonia production. If this study showed better results in terms of prevention of hepatic

encephalopathy by the combined use of Rifaximin and Lactulose, it might help us to reduce mortality in Chronic Liver Disease patients secondary to Hepatic Encephalopathy and decrease burden of indoor patients in our overloaded hospitals.

RESEARCH METHODOLOGY

This descriptive cross sectional study was conducted at Department of Medicine, DHQ Hospital, Pakpatan from June 2015 to May 2016. Total 98 patients with chronic liver disease with duration of liver at least 6 month, either male or female having age from 20-60 years were selected for this study. Exclusion criteria was: the expectation of liver transplantation within 1 month after the screening visit. The presence of conditions that are known precipitants of hepatic encephalopathy (Gastrointestinal hemorrhage within 3 months before the screening visit, Chronic renal insufficiency (creatinine level, >2.0 mg per deciliter), Respiratory insufficiency, Anemia (hemoglobin level, <8 g per deciliter), An electrolyte abnormality (serum sodium level, <125 mEqper liter; serum calcium level, >10 mg per deciliter [2.5mmol per liter]; or potassium level, <2.5 mmol per liter), Inter-current infection, or active spontaneous bacterial peritonitis[4]).

OPERATIONAL DEFINITIONS:

Chronic Liver Disease: CLD was diagnosed on ultrasonography with small size liver (size<13 cm) having coarse texture liver and having one of the following in addition:

Portal vein diameter >10mm.

Splenomegaly: size of spleen (length)> 13 cm on ultrasound.

Ascites: shifting dullness +ve and confirmed on ultrasound.

Hepatic Encephalopathy: Hepatic encephalopathy was assessed by Conn score[10](based on history and clinical examination) as follows;

0 = no personality or behavioral abnormality on clinical assessment.

1 = Day-night sleep pattern disturbance (contrary to patient's previous sleeping routine, he or she remains awake during night and sleeps in the morning), impairment of ability to add or subtract (unable to sequentially subtracting 7 starting from 100).

2 = Disorientation in time (at least three of the followings are wrong: day of the month, day of the week, month, season or year), obvious personality changes, flapping tremors in hands (on clinical assessment).

3= Disoriented also for space (considered positive if patient wrongly reported city or place), responsiveness only on stimulus.

4 = coma (non-responsiveness even to painful stimuli).

Hepatic Encephalopathy was taken as positive if Conn's score was ≥2.

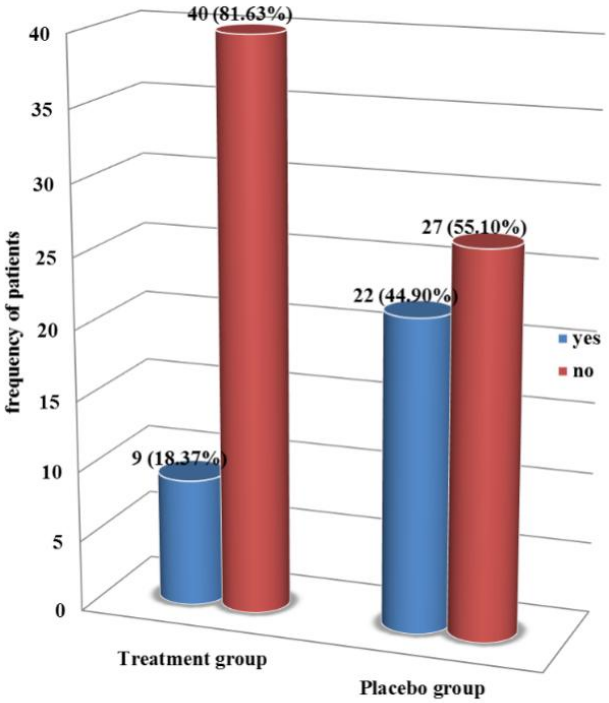
Recurrence was taken as positive if patient of hepatic encephalopathy of Conn's score ≥2 was presented again within 3 months after discharge from ward with Conn's score <2.

Patients randomly divided into two groups i.e. treatment and placebo groups for the study using random numbers generated from random table. Treatment group patients were advised to take tab Rifaximin 550 mg twice daily along with standard prescription i.e. Lactulose 30 to 60 ml in two to three divided doses per day. Placebo group was prescribed only conventional treatment i.e. Lactulose 30 to 60 ml in two to three divided doses per day. All patients were discharged from ward after hepatic encephalopathy Conn's score was<2. Enrolled patients were followed for 3 months at which final outcome i.e., recurrence of hepatic encephalopathy (yes/no) was noted. All this data was recorded on a predesigned proforma.

Data collected was entered and analyzed in the SPSS version 19. Mean and SD was calculated for numerical data and frequencies and percentages were calculated for categorical data.

RESULTS

Fig. 1: Comparison of recurrence of HE between the both groups



Age range in this study was from 20 to 60 years with mean age of 43.68±10.87 years. The mean age of patients in treatment group was 43.76±10.54 years and in placebo group was 43.65±11.13 years. Recurrence of hepatic encephalopathy was seen in 9(18.37%) patients in treatment group and 22(40.90%) patients in placebo group and difference for recurrence of HE was statistically significant with p-value of 0.005 as shown in Figure 1. Stratification of patients according to duration of disease was done and two groups was made i.e. ≥6 – <12 months duration of disease and >12 months duration of disease. Recurrence of HE was 06 (17.65%) and 16 (44.44%) was noted in both treatment groups respectively in ≥6 – <12 months duration of disease group. Difference of recurrence rate in both group was statistically significant with p value 0.016. In patients having duration of disease >12 years, Recurrence of HE was noted in 03 (20.0%) and 06 (46.15%) patients respectively. Difference of recurrence of HE between the both groups was insignificant with p value 0.139. (Table 1) Patients were divided into four age groups i.e. 20-30 years, 31-40 years, 41-50 years and 51-60 years. In age group 20-30 years, recurrence of HE was noted in 02 (28.57%) patients and 03 (37.50%) patients in both treatment groups. Difference for recurrence of HE was insignificant between the both groups with p value 0.714. In age group 31-40 years, recurrence of HE was noted in 03 (25.0%) patients and 07 (58.33%) patients in both groups and difference of recurrence rate of HE was insignificant with p value 0.098. Recurrence of HE was observed in 02 (14.29%) patients and 04 (33.33%) patients in age group 41-60 years but the difference was also insignificant with p value 0.250. In age group 51-60 years, recurrence of HE was seen in 02 (12.50%) patients and 08(47.06%) patients and the difference was statistically significant with p value 0.031. (Table 2) Recurrence of HE was observed in 07 (19.44%) male patients and 15 (45.45%) male patients and difference of recurrence rate between the both groups was statistically significant with p value 0.021. In female patients, recurrence of HE was noted in 02 (15.38%) patients and 07 (43.75%) patients respectively in both treatment groups and the difference was insignificant with p value 0.101 (Table 3).

Table 1: Stratification in relation to duration of disease

Duration of disease (months)	**Treatment group (n=49)**		**Placebo group (n=49)**		**p-value**
	Yes	**No**	**Yes**	**No**	
≥6 – <12	06 (17.65%)	28 (82.35%)	16 (44.44%)	20 (55.56%)	**0.016**
>12	03 (20.0%)	12 (80.0%)	06 (46.15%)	07 (53.85%)	**0.139**

Table 2: Stratification in relation to age

Age of patients	**Treatment group (n=49)**		**Placebo group (n=49)**		**p-value**
	Yes	**No**	**Yes**	**No**	
20-30	02 (28.57%)	05 (71.43%)	03 (37.50%)	05 (62.50%)	0.714
31-40	03 (25.0%)	09 (75.0%)	07 (58.33%)	05 (41.67%)	0.098
41-50	02 (14.29%)	12 (85.71%)	04 (33.33%)	08 (66.67%)	0.250
51-60	02 (12.50%)	14 (87.50%)	08 (47.06%)	09 (52.94%)	0.031

Table 3: Stratification in relation to gender

Gender	**Treatment group (n=49)**		**Placebo group (n=49)**		**p-value**
	Yes	**No**	**Yes**	**No**	
Male	07 (19.44%)	29(80.56%)	15(45.45%)	18 (54.55%)	0.021
Female	02 (15.38%)	11(84.62%)	07 (43.75%)	09 (56.25%)	0.101

DISCUSSION

The purpose of this study was to compare the frequency of recurrence of HE in cirrhotics treated with Rifaximin plus Lactulose versus conventional oral treatment with Lactulose alone. In our study, recurrence of hepatic encephalopathy was seen in 18.37% patients in treatment group and 40.90% patients in placebo group with p-value of 0.005.

In one study rate of recurrence of HE was 22.1% in cases treated with rifaximin as compared to placebo group (45.9%).[4] Rifaximin, by contrast, has emerged as an effective treatment strategy to prevent recurrence of HE in a multicenter study.[11] In another study, Rifaximin was advised for the treatment of HE which proved excellent results as compared to placebo group.[12] A study by Sharma et al evaluated 120 patients with overt HE (>80% grade 3 or 4) who were randomized to receive either lactulose alone or lactulose + rifaximin. Of these cases, 55 had experienced previous episodes of HE requiring

treatment, but no patients were refractory to treatments[13].

In another study, total number of hospitalizations during the rifaximin phase was fewer than during the lactulose phase (17 vs. 60 days). This translated to an 87% reduced risk for hospitalization associated with receiving rifaximin compared to lactulose (OR=0.13; 95% CI 0.05-0.4; p<0.001)[14]

A significantly greater percentage of patients in the combination group experienced a reversal of HE compared to lactulose (76% vs. 44%, p=0.004). Combination rifaximin and lactulose also significantly reduced the length of hospital stay (5.8 days vs. 8.2 days, p=0.001) and mortality rate (24% vs. 49%, p<0.05) compared to lactulose alone[15].

CONCLUSION

This study concluded that Rifaximin plus Lactulose is better in reducing the recurrence of hepatic encephalopathy as compared to conventional treatment with Lactulose alone. So, we recommend that Rifaximin plus Lactulose should be used as a primary treatment method in hepatic encephalopathy for reducing its recurrence.

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